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Perspective

Regulation of herbal medicine use based on speculation? A case from Sri Lanka

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ABSTRACT

Chronic Kidney Disease of Unknown aetiology is a significant public health problem in Sri Lanka. The final report by the WHO mission recommended regulation of herbal medicines containing aristolochic acid, which is an established nephrotoxin. The use of Complimentary and Alternative Medicine (CAM) has a history of more than 2500 years in Sri Lanka. *Aristolochia* species are rarely used in Ayurveda and traditional medicine in Sri Lanka. Before regulating the analysis of herbal preparations using *Aristolochia*, collecting data from CAM practitioners regarding the use of *Aristolochia* is necessary. Analysis of Ayurveda pharmacopeia shows the doses used are negligible and some preparations are used for external applications.

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The recent emergence and rapid spread of Chronic Kidney Disease of Unknown aetiology (CKDu) or Chronic Interstitial Nephritis in Agricultural Communities (CINAC) in Sri Lanka necessitated immediate action to identify the cause to control it. Several groups hypothesized environmental toxins, including heavy metals found in agrochemicals, as causative agents^{1,2} including the special mission on CKDu appointed by the World Health Organization.³ The final report by the WHO mission mentioned ten recommendations to protect the public from CKDu.⁴ The sixth recommendation states “regulate the use of herbal medicines containing aristolochic acid as it is an established nephrotoxin which has been shown to cause kidney disease in other parts of the world”. This is probably based on the fact that aristolochic acid, consumed in the form of herbal products is associated with the Aristolochic acid nephropathy.⁵ Chronic tubulo-interstitial nephropathy and

urothelial carcinoma seen in Balkan nephropathy is also associated with aristolochic acid.⁶ In our view, linking of aristolochic acid containing herbal medicine preparations to CKDu warrants further discussion.

Sri Lankans from all geographical regions are using complementary and alternative medicine (CAM) since ancient times.^{7,8} Recent studies indicates 1.2–3% patients are seeking ayurvedic treatment.^{9,10} The CKDu with increasing prevalence during the last two decades causes significant burden and seen mainly in the North Central Province.^{2,3} Aristolochic acid is an alkaloid compound naturally contained particularly in the genus *Aristolochia*.¹¹ Various parts of the *Aristolochia* species have been used as anti-inflammatory, diuretic and oedema reducing agents by practitioners of the Chinese traditional medicine.¹¹ Three species of *Aristolochia* vines namely, *indica*, *bracteolata*, and *ringens* are found in Sri Lanka. While *Aristolochia indica* and *A. bracteolata* (“Sapsanda” in Sinhalese) are considered native to Sri Lanka, *A. ringens* was introduced as an ornamental plant. Although both *A. indica* and *A. bracteolata* are used as ingredients of medicinal preparations in CAM systems in Asia, only *A. indica* is used in Ayurveda and traditional medicine in Sri Lanka. *A. bracteolata* is listed as a near

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threatened plant species in Sri Lanka, hence use of this in Ayurvedic medicine is questionable.¹²

Use of *A. indica* in standard Ayurvedic preparations in Sri Lanka is sparse (personal communication with practitioners of Ayurveda) and out of many hundreds of recipes in the Ayurveda pharmacopeia published by the government of Sri Lanka, only ten preparations contain 'sapsanda' (*A. indica*) as an ingredient (see Table 1).¹³ In the list there are two "kashaya" (herbal decoction), one "kwatha" (Alcohol based infusion) and six "thaila" (herbal oil) and one "guliya" (herbal pill). Herbal oils are used mainly externally and from the list of six herbal oils, four containing *A. indica* are used both externally and internally. Despite being listed in the pharmacopeia, the preparations recommended for internal use are not commonly prescribed in the current practice of Ayurveda medicine in Sri Lanka.

Traditional medical texts such as *Vatikaparakaranaya* claims of many medicinal properties of *A. indica* including anti-inflammatory, anti-microbial and anti-ulcer activities.¹⁴ 'Sapsanda' is mainly mentioned as an ingredient of herbal decoctions and external applications used for snakebite management in the indigenous system of medicine in Sri Lanka.¹⁵

Whenever *Aristolochia* species is used in Sri Lanka, it is an ingredient of a poly-herbal compound rather than used as a single herb. It is widely known that poly-herbal compounds which undergo complex manufacturing processes may not unequivocally possess the characteristics, qualities and undesired side effects of the individual ingredients.¹⁶ Hence there is no established evidence to suggest that whatever the poly-herbal compounds used in Sri Lanka that contains *Aristolochia* as an ingredient, would have aristolochic acid in considerable concentrations after processing. Aristolochic acids are very polar compounds and therefore, their

concentration in end product depends also on the other ingredients used. Moreover, being a secondary metabolite in plants, the amount of aristolochic acid present in a unit weight of plant material depends on a variety of factors such as the place where the plant was growing (latitude, temperature etc.), age of the plant, plant parts used, time and method of harvesting, storage conditions etc.^{17,18} Further there is no data on Ayurvedic and traditional medicines used in Sri Lanka containing extracts of *Aristolochia*, being tested for the presence of aristolochic acid. The presence of high amounts of aristolochic acid in *Aristolochia fangchi*, used in slimming herbal preparation consumed by Belgians,¹⁹ in *A. manshuriensis* which was almost banned to be used in traditional Chinese medicine²⁰ and in *A. clematitis* which is hypothesized to be the cause of Balkan endemic nephropathy²¹ does not imply the existence of similar risk with *A. indica* in Sri Lanka. Even though the potential risks associated with the use of *A. indica* was assessed, no cases of Aristolochic acid nephropathy (AAN) have been reported in Bangladesh where *A. indica* is widely available in herbal markets and through healers networks.²²

Oral intake of the cumulative doses above 200 g of herbal preparations of *Aristolochia* for a mean duration of 15 months is shown as a risk factor for urothelial carcinoma and for the development of Aristolochic acid nephropathy, oral intake of cumulative dose of aristolochia preparations over 150 g for a mean duration of 12 months is needed.²³ Toxicity studies using animal models have proved even very high doses (up to 3000 mg/kg) of ethanol extract and 5000 mg/kg of aqueous root extract of *A. indica* as safe when used for a short period.^{24,25}

Even when used sparsely, CAM systems in Sri Lanka uses much lower doses of *Aristolochia* preparations than known to be associated with tubulo-interstitial nephropathy or urothelial carcinoma.

Table 1
Ayurvedic herbal preparations.¹³

Name (page in Ref. 9)	Preparation	Contents	Daily dose	Recommended duration	Total dose	Indication
Valu Kashaya (1) Page 111	Decoction	One out of 12 herbs	1.68 g	3 days	5 g	Puerperal psychosis
Valu kashaya (2) Page 112	Decoction	One out of 19 herbs	1.25 g	3 days ^b	3.75 g	Puerperal psychosis
Vasa Musthakadi kwathaya (1) Page 112	Alcohol based infusion	One out of 19 herbs	3.75 g	Few days or one week ^b	26.25 g	Diarrheal infections and sepsis
Abing Guliya Page 140	Pill	One of 23 ingredients	5.43 mg	Up to one week ^b	38 mg	Anti-helminthic and in diarrhea
Yama Devaraja Thailaya Page 252	Herbal oil	One out of 54 ingredients	7.85 mg	Up to one week ^b	55 mg	External-nasal polyps and tonsillitis. Internal-diphtheria and tonsillitis
Maha Vayurakshasa thailaya Page 251	Herbal oil	One out of 19 ingredients	62.5 mg	3–4 days ^b	250 mg	Neurological disorders, facial nerve palsy, puerperal psychosis cerebral oedema
Vishagarbha thailaya Page 257	Herbal oil	External use only for rheumatological conditions				
Neelaraja Thailaya Page 241	Herbal oil	One out of 31 ingredients	64.25 mg	Single dose ^b	64.3 mg	Scorpion and snakebite
Navapatala Thailaya Page 238	Herbal oil	External use only for headache, migraine, sinusitis and eye diseases				
Dashavaga prameha thailaya Page 236	Herbal oil	One out of 65	6.9 mg ^a	Two weeks ^b	96.6 mg	Urinary tract disorders, hemorrhoids, headaches and neurological disorders

^a The daily dose is not mentioned in the pharmacopeia. Dose is decided based on commonly used doses in practice or as assumed by authors.

^b The duration is not mentioned in the pharmacopeia. Duration is decided based on the general practices of using such drugs and the duration of illnesses that are treated.

The maximum total dose that a patient is exposed to aristolochic acid in an Ayurvedic herbal preparation is 26.25 g (Table 1). Further, in CAM, exposure of patients to *A. indica* is likely to be of very short term, particularly when used for snakebites. Extensive literature search failed to locate a single clinical report of chronic kidney disease from Sri Lanka, attributed to *Aristolochia* consumption from CAM treatment or uroepithelial cancer associated with CKDu. A publication that arose from the WHO study explicitly says that the long-term use of herbal medicines was seen in a very small percentage of CKDu patients.³

Therefore, we argue that the available information is inadequate to recommend regulation of the herbal preparation containing aristolochic acid in Sri Lanka as a control measure of CKDu. We further feel that caution should be practiced when such non-evidence based recommendations are made in a country like Sri Lanka where CAM systems are currently widely practiced and in existence for more than 2500 years. This again emphasizes the need for research into CAM systems that is integrated with (in this specific example) principals and philosophies of Ayurveda.²⁶ Analyzing the concentration of aristolochic acid, using reproducible, accurate analytical methods, in herbal preparations using *Aristolochia* as one of the ingredients, collecting data from drug manufactures and Ayurveda practitioners regarding the use of *Aristolochia* in traditional medicine recipes other than Ayurveda pharmacopeia and analyzing relevant clinical data to evaluate the relationship (if any) between CKDu and aristolochic acid in Sri Lanka is a must.

Conflict of interest

None declared.

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